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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/904,557	07/16/2001	Takahiko Ishiguro	Q65441	6024

7590 05/17/2006

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EXAMINER

SHAW, AMANDA MARIE

ART UNIT	PAPER NUMBER
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1634

DATE MAILED: 05/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/904,557	ISHIGURO ET AL.	
	Examiner	Art Unit	
	Amanda M. Shaw	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 20 March 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 13-16 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 13-16 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>7/16/01, 5/31/02</u> | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/20/06 has been entered.

Claims 13-16 are pending and claims 13, 14, and 16 have been amended to make clear that the recited method is repeated on different portions of the DNA sample. This Office action contains new grounds of rejection and is made non-final.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13-14 and 16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to

one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection

In the instant case the specification does not appear to provide support for the amendment which recites the step of repeating steps A and B on a selected DNA molecule "that is different from the selected portion of (B)". The claim language encompasses methods in which (i) a region is selected for testing and then the testing is repeated on an entirely different region (ii) and methods in which a region is selected for testing and then the testing is repeated using the same region but a different portion of that region. It is noted that the applicant points to the specification at page 5, line 23 through page 6 line 2 for support. The specification states "A seventh embodiment of the invention is a method for determining the gene expression region in an arbitrary region on a genome or the entire genome, which comprises repeatedly carrying out the method of the first to sixth inventions". Thus the specification provides support for repeating steps A and B but does not provide support for repeating on a different portion of the selected DNA molecule. Additionally the applicant points to the specification at pages 15-17 for support. Here the specification teaches that a region composed of 900 base pairs was divided into five specific regions each having 180 base pairs and that primer and probe sets were made for each region. However the specification does not provide support for selecting a region for testing and then repeating the testing using the same region but a different portion of that region.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

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The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 13-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 13-16 are indefinite over the recitation of the phrase "that is different from the selected portion of (B)". It is not clear whether the method requires one to select a region to be tested and then repeat the method on an entirely different region or if the method requires one to select a region to be tested and then repeat the method using the same region but a different portion of that region. The claims are also indefinite over the recitation of "corresponding to a selected portion of". Corresponding is not an art recognized term to describe the relationship between two nucleic acid sequences or two amino acid sequences. It is not clear as to whether a corresponding nucleic acid refers to a nucleic acid residue which is at the same position or to a nucleic acid residue which is at a nearby position or if this refers to a similar nucleic acid residue or the same nucleic acid residue at any position. Because the term "corresponding" has not been clearly defined in the specification and because there is no art recognized definition for this term as it relates to nucleic acid sequences, one of skill in the art cannot determine the meets and bounds of the claimed subject matter. Additionally the phrase "a selected portion of" is considered indefinite because the phrase is not clearly defined in the specification and there is no art recognized definition for this phrase. For example, it is unclear as to whether "a selected portion of" is any portion of any DNA sequence that has been selected by virtue of amplifying it or a portion of a specific DNA sequence.

Claims 13-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite in that the goal of the method and the final step do not agree. Claim 13 is drawn to a method for determining whether a selected DNA molecule encodes a gene expression region. However, the claims recite the final step of detecting an amplification product. The steps listed in the method do not result in determining whether a selected DNA molecule encodes a gene expression region. Therefore, it is unclear as to whether the claims are intended to be limited to methods for determining whether a selected DNA molecule encodes a gene expression region or methods for detecting an amplification product.

Claims 16 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite in that the goal of the method and the final step do not agree. Claim 16 is drawn to a method for determining which portion of a selected DNA molecule encode a gene expression region. However, the claims recite the final step of screening the RNA transcripts. The steps listed in the method do not result in determining which portion of a selected DNA molecule encodes a gene expression region. Therefore, it is unclear as to whether the claims are intended to be limited to methods for determining which portion of a selected DNA molecule encode a gene expression region or methods for screening RNA transcripts.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 16 is rejected under 35 U.S.C. 103(b) as being anticipated by Lockhart et al (US Patent 6040138).

Lockhart et al teach a method for monitoring the expression levels of a multiplicity of genes. The method involves providing a pool of target nucleic acids comprising RNA transcripts of one or more target genes, hybridizing said pool of nucleic acids to an array of oligonucleotide probes immobilized on surface, where the array comprising more than 100 different oligonucleotides and each different oligonucleotide is localized in a predetermined region of the surface, and quantifying the hybridized nucleic acids in the array. This method can be used to determine if the DNA molecule encodes a gene expression region. In the method of Lockhart, portions of the RNA probes come from the same chromosomal DNA and thereby the method of Lockhart is considered to be one which assays for different RNA transcripts from a selected chromosomal DNA molecule. It is noted that the claim has been interpreted such that the repeating step of (c) may occur simultaneously with performing steps a and b (i.e., in the Lockhart reference each of the RNA transcripts are simultaneously analyzed). As written the claims are not limited to doing steps a and b and then doing step c; but rather the claims include doing steps a and b, simultaneously with step c.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Davey et al. (US Patent 5,409,818) in view of Cao (US Patent 6582906).

As noted in the MPEP 211.02, "a preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone." Further, in *Pitney Bowes Inc. v. Hewlett-Packard Co.*, 182F.3d 1298, 1305, 51 USPQ2d 1161, 1166 (Fed Cir. 1999) the court held that if the body of the claim sets forth the complete invention, and the preamble is not necessary to give "life, meaning and vitality" to the claim, "then the preamble is of no significance to claim construction because it cannot be said to constitute or explain a claim limitation." In the present situation, the method steps of the claimed invention are able to stand alone and the preamble limitation is not accorded patentable weight. Accordingly, the claim language of "method for determining whether a selected DNA molecule encodes a gene

expression region" merely sets forth the intended use or purpose of the claimed method, but does not limit the scope of the claims.

With regard to claim 13 Davey et al. teach a method for determining whether a selected DNA molecule encodes a gene expression region which in this case is a 92 bp segment of the gag portion of the HTLV-III genome, the causative agent of AIDS (Col. 12 lines 33-35), said method comprising:

- (A) obtaining RNA transcripts from an organism (ultimately HIV-1 virus, also *E. Coli*, Col. 11 line 50) which comprises said selected DNA molecule,
- (B) screening said RNA transcripts for an RNA transcript corresponding to a selected portion of said selected DNA molecule, wherein the nucleotide sequence of said selected portion of said selected DNA molecule is known, to thereby determine whether said selected portion of said selected DNA molecule encodes a gene expression region such as the 92 bp segment of the gag portion of the HTLV-III genome (Col. 12 lines 33-35), wherein said screening comprised:

- (i) amplifying the RNA transcripts using a first oligonucleotide primer and a second oligonucleotide primer, wherein said first primer is complementary to a sequence of at least 10 continuous nucleotides located at or near the 3'-end of said selected portion of said selected portion of said selected DNA molecule, and said second primer is homologous to a sequence of at least 10 continuous nucleotides located at or near the 5'-end of said selection portion of said selected DNA molecule (See Figure 1 and Col. 5 lines 14-25, Col. 6 lines 19-68 for example), and

(a) forming a RNA-DNA duplex comprising one of said RNA transcripts and a complementary DNA molecule adhered thereto, said duplex is formed by synthesizing a first DNA molecule complementary to at least a portion of one of said RNA transcripts using (1) said first oligonucleotide primer to prime synthesis of said first DNA molecule, (2) RNA-dependent DNA polymerase and (3) one of said RNA transcripts as a template, to thereby form an RNA-DNA duplex as can be seen in Figure 1 and Col. 5 lines 27-35 for example.

(b) preparing a single stranded DNA molecule from said RNA-DNA duplex of (e) by hydrolyzing the RNA transcript of said RNA-DNA duplex using ribonuclease H(Col. 8 lines 20-33 for example).

(c) forming a doubled-stranded DNA molecule comprising the single-stranded DNA molecule of (f) and a complementary DNA molecule thereto, said doubled-stranded DNA molecule is formed by synthesizing a second DNA molecule complementary to at least a part of said single-stranded DNA molecule of (f) using (1) said second oligonucleotide primer to prime the synthesis of said second DNA molecule, wherein said second primer further comprises an RNA-transcriptable promoter sequence at its 5'-end, (2) DNA-dependent DNA polymerase, and (3) the single-stranded DNA molecule of (f) as a template, to thereby form a double stranded DNA molecule as can be seen in Figure 1 and further in Col. 4 lines 10-15.

(d) forming an RNA transcription product from said double-stranded DNA molecule of (g) using RNA polymerase, wherein RNA transcription is primed from the RNA-transcriptable promoter sequence(Col. 7 lines 28-47 for example).

(e) repeating steps (a) to (d) using said RNA transcription product of (d) as a template for the formation of the RNA-DNA duplex of (a)(Col. 19 claim 1(C)).

(ii) detecting an amplification product of (i) corresponding to said selected portion of said DNA molecule, to thereby screen said RNA transcripts for an RNA transcripts for a RNA transcript that corresponds to said selected portion of said selected DNA molecule via the incorporation of a labeled precursor into the amplification process(Col. 6 lines 4-6 and Col. 8 lines 47-67 for example).

(C) repeating (A) and (B) on at least one other selected portion of said selected DNA molecule(Col. 3 lines 26-58, where the reference teaches that a “plurality of copies of the RNA sequence of the first template from the third template” can be synthesized).

Davey et al does not teach repeating (A) and (B) on at least one other selected portion of said selected DNA molecule that is different from the selected portion of (B).

However Cao teaches method used to analyze gene expression in which the method steps are repeated using a different portion of the selected DNA molecule. Specifically Cao et al teaches a method for amplification of a population of nucleic acids comprising; (i) synthesizing a single-stranded DNA population from said population of RNA; (ii) separating the DNA from the DNA/RNA hybrid using heat or an enzyme treatment, (iii) fragmenting the single-stranded cDNA to produce a fragmented single-stranded cDNA population; (iv)synthesizing double-stranded DNA from the fragmented single-stranded cDNA population; (v) and producing multiple copies of sense RNA from

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said double-stranded DNA (Column 6, Claim 1). Cao also teaches that methods of the present invention are repeated once or multiple times (Column 3). As a result each time the method is repeated the starting population of RNA is different because the cDNA in step (iii) is fragmented and therefore produces a population of different dsDNA sequences which encode of a population of different mRNAs.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Davey et al so as to have repeated the methods steps on different portions of RNA in order to have achieved the benefits set forth by Cao of providing a method which overcomes having to analyze long templates for gene expression which can be difficult and less efficient due to interference from secondary and tertiary structure in the template.

Response to Arguments:

In the response filed March 20, 2006, Applicants traversed this rejection by stating that the new claims recite a step of repeating the amplification method on a different portion of the selected DNA molecule. The response states that this limitation is not disclosed in the Davey reference.

This argument has been fully considered and has been found persuasive because while Davey does not teach the concept of repeating the method on a different RNA region, the rejection is not based on the teachings of Davey alone. Rather, Cao has been cited as teaching methods in which multiple regions of an RNA molecule are analyzed. Accordingly, in view of the teachings of Cao, it would have been obvious to modify method of Davey so as to have repeated the methods steps on different portions of RNA in order to have achieved the benefits set forth by Cao of providing a method which overcomes having to analyze long templates for gene expression which can be difficult and less efficient due to interference from secondary and tertiary structure in the template.

Additionally, Applicants traversed this rejection by stating that the claims are drawn to methods for determining whether a selected DNA molecule encodes a gene expression region. The response states that this is not disclosed in the Davey reference.

This argument has been fully considered but is not persuasive because Davey et al does in fact teach a method comprising the step of expressing a product encoded by said DNA product (See Claim 40). Additionally, the claim language of "method for determining whether a selected DNA molecule encodes a gene expression region" merely sets forth the intended use or purpose of the claimed method, but does not limit the scope of the claims.

5. Claims 14 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davey et al. (US Patent 5,409,818) in view of Cao (US Patent 6582906) and in further view of Wittwer et al.(US Patent 6,503,720 B2).

The teachings of Davey et al and Cao et al are presented above.

The combined references do not teach that the amplification product is detected using an oligonucleotide probe that is labeled with an intercalating fluorescence dye and with respect to claim 15 an intercalating fluorescence dye that has a differential fluorescence characteristic depending on whether said probe exists in an unbound single-stranded state or in a bound duplex with said amplification product.

However, Wittwer et al. (US Patent 6,503,720 B2) teach such an intercalating probe in their teaching of amplification by PCR and subsequent detection with SYBR green in Example 2, Col. 9-10 and further teach an intercalating fluorescence dye that has a differential fluorescence characteristic depending on whether said probe exists in an unbound single-stranded state or in a bound duplex with said amplification product in Col. 7 lines 6-19 for example when they assert that using their Taq Man principle detects an amplification product, which is labeled with a fluorescent entity, the fluorescence emission of which is quenched by a second label in its un-hybridized form and upon its hybridization to its target sequence and following digestion with a DNA polymerase having a 5'-3' exonuclease activity, lacks quencher and therefore fluoresces in its hybridized state as compared to its un-hybridized form. In addition, in Col. 4 lines 7-10, Wittwer specifically teaches that "within the scope of the invention, are different methods for amplifying nucleic acids, for example NASBA (WO 91102814)" which

applicant themselves teach in their specification on page 11 line 6 and further in their examples as an embodied method of RNA amplification.

Therefore, It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the methods of Davey et al and Cao et al with the use of SYBR Green, intercalating based fluorescent probes of Wittwer et al. for the expected benefit derived from the Wittwer et al. probe that allows for the concentration of an amplifiable or replicable analyte being determined without correction for different fluorescent backgrounds (Col. 2 lines 22-24) and further “provides such an independence of absolute signal level for systems wherein multiple fluorescent signals being detected through multiple channels with different window ranges may be compared”(Col. 2 lines 30-34). Furthermore, the motivation to combine the references existed since Davey’s 3SR method of RNA amplification (also know as NASBA) was taught by Wittwer et al. to be “within the scope of the invention” as it is a “different method for amplifying nucleic acids, for example NASBA(WO 91102814)” as taught by Wittwer et al. in Col. 4 lines 7-10.

Response to Arguments:

In the response filed March 20, 2006, Applicants traversed this rejection by stating that the new claims recite a step of repeating the amplification method on a different portion of the selected DNA molecule. The response states that this limitation is not disclosed in the Davey or Whittwer references.

This argument has been fully considered and has been found persuasive because Davey and Whittwer both do not teach the concept of repeating the method on a different RNA region, the rejection is not based on the teachings of Davey and Whittwer alone. Rather, Cao has been cited as teaching methods in which multiple regions of an RNA molecule are analyzed. Accordingly, in view of the teachings of Cao, it would have been obvious to modify method of Davey so as to have repeated the methods steps on different portions of RNA in order to have achieved the benefits set forth by Cao of providing a method which overcomes having to analyze long templates for gene expression which can be difficult and less efficient due to interference from secondary and tertiary structure in the template.

6. No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda M. Shaw whose telephone number is (571) 272-8668. The examiner can normally be reached on Mon-Fri 7:30 TO 4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Amanda M. Shaw
Examiner
Art Unit 1634
May 15, 2006


CARLA J. MYERS
PRIMARY EXAMINER